Supporting Information for:

Convergency and Divergency as Strategic Elements in Total Synthesis: The Total Synthesis of (–)-Drupacine and the Formal Total Synthesis of (±)-Cephalotaxine, (–)-Cephalotaxine and (+)-Cephalotaxine

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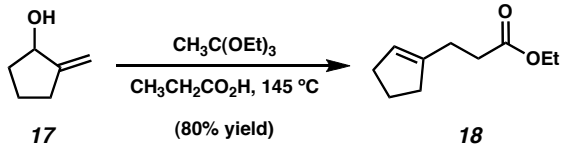
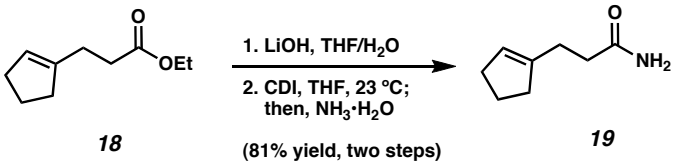
Materials and Methods. Unless stated otherwise, reactions were performed in flame-dried glasswares under a nitrogen or an argon atmosphere, using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All other commercially obtained reagents were used as received. Reaction temperatures were controlled by a temperature modulator. Thin-layer chromatography (TLC) was conducted with silica gel pre-coated plates (0.25 mm) and visualized using a combination of UV, *p*-anisaldehyde and ceric ammonium molybdate. Preparative TLC was conducted with silica gel pre-coated plates (0.50 mm, 20 × 20 cm). Silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral HPLC was performed with a Chiralcel AD, AS, OJ or OD-H normal phase column (each is 4.6 mm × 25 cm). ^{1}H NMR spectra were recorded at 300 MHz or at 500 MHz and are reported relative to residual solvent peaks ($CDCl_3$, δ 7.26; DMSO-d_6, δ 2.49). Data for ^{1}H NMR spectra is reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded at 75 MHz or at 125 MHz and are reported relative to residual solvent peaks ($CDCl_3$, δ 77.3; DMSO-d_6, δ 39.5). Data for ^{13}C NMR spectra is reported in terms of chemical shift. IR spectra were recorded on a spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured with a polarimeter. High resolution mass spectra were obtained.

Preparative Procedures.

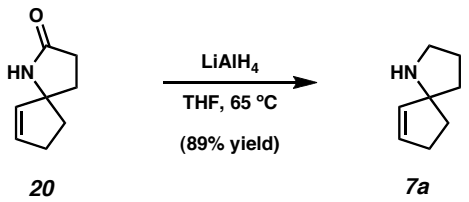


Ester 18. The allylic alcohol **17** (12.3 g, 125 mmol) was dissolved in triethylorthoacetate (150 mL, 818 mmol), and the solution was treated with propionic acid (3.0 mL, 40 mmol). The reaction was heated to 145 °C with distillative removal of ethanol (ca. 23 mL). After distillation was complete, the reaction was stirred at 145 °C for an additional 1 h, and then cooled to room temperature and diluted with Et_2O (300 mL). The resulting solution was stirred with 1.0 M aqueous $KHSO_4$ (300 mL) for 8 h. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 300 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (300 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (30:1 hexanes/ Et_2O) to give ester **18** (16.6 g, 80% yield) as a clear oil. R_f 0.62 (4:1 hexanes/ Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.32 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 2.47-2.41 (m, 2H), 2.38-2.32 (m, 2H), 2.30-2.19 (m, 4H), 1.83 (quintet, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 143.2, 124.1, 60.5, 35.3, 33.1, 32.6, 26.6, 23.6, 14.4; IR (neat): 2943, 1736, 1445, 1184, 1038 cm^{-1}; HRMS-EI (m/z): $[M]^+$ calc'd for $C_{10}H_{16}O_2$, 168.1150; found, 168.1155.



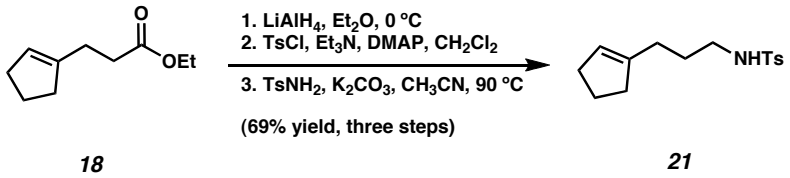
Amide 19. To a solution of ethyl ester **18** (3.0 g, 17.8 mmol) in THF (30 mL) at room temperature was added a solution of LiOH (2.13 g, 89.0 mmol) in H_2O (30 mL). The mixture was heated to 50 °C and stirred for 15 h. The mixture was cooled to room temperature, and the volatile solvent was removed by rotary evaporation. The aqueous residue was acidified to pH = 0 with 3 N HCl. The white solid (2.1 g, 84.2%) was collected by vacuum filtration. R_f 0.35 (4:1 hexanes/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.5 (br s, 1H), 5.37 (app. quintet, J = 1.8 Hz, 1H), 2.55-2.50 (m, 2H), 2.42-2.36 (m, 2H), 2.33-2.22 (m, 4H), 1.86 (app. quintet, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.2, 142.8, 124.3, 35.4, 32.8, 32.7, 26.3, 23.6; IR (film): 3100 (br), 2896, 1706, 1446, 1302 cm^{-1}.

To a solution of acid (4.65 g, 33.2 mmol) in THF (100 mL) was treated with 1,1'-carbonyldiimidazole (CDI, 5.43 g, 33.5 mmol) at room temperature. After stirring for 1 h, the solution was cooled to 0 °C and 28% ammonium hydroxide solution (12 mL) was added in one portion. The solution was sparged with argon to remove excess ammonia and the volatile solvent was removed by rotary evaporation. The resulting white solid was suspended in H_2O (100 mL) and collected by vacuum filtration to give the amide **19** (4.5 g, 97.5% yield) as a white powder. R_f 0.15 (1:1 hexanes/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (br s, 1H), 5.58 (br s, 1H), 5.38 (br s, 1H), 2.39 (app. s, 4H), 2.32-2.22 (m, 4H), 1.86 (app. quintet, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 143.3, 124.5, 35.3, 34.4, 32.6, 27.0, 23.6; IR (film): 3382, 3183, 1657, 1632, 1416 cm^{-1}; HRMS-EI (m/z): $[M]^+$ calc'd for $C_8H_{13}NO$, 139.0997; found, 139.0996.



20 *7a*

Spiroamine 7a. To a suspension of lithium aluminum hydride (417 mg, 11.0 mmol) in THF (10 mL) at 0 °C was added a solution of spirolactam **20** (504 mg, 3.68 mmol) in THF (8 mL) dropwise over 2 min. The reaction mixture was heated to 70 °C and stirred for 8 h. The mixture was cooled to 0 °C and quenched with H_2O (0.42 mL), 3 N NaOH (0.42 mL) and H_2O (0.85 mL) sequentially. The mixture was allowed to warm to room temperature and stirred vigorously for 4 h. The resulting white precipitate was removed by vacuum filtration and the filtrate was concentrated in vacuo to provide amine **7a** (402 mg, 89% yield) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.65 (dt, J_1 = 5.7 Hz, J_2 = 2.4 Hz, 1H), 5.55 (dt, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H), 2.88 (td, J_1 = 6.9 Hz, J_2 = 1.8 Hz, 2H), 2.36-2.15 (m, 3H), 1.87-1.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 131.1, 74.2, 46.0, 38.6, 37.6, 31.3, 25.7; IR (film): 3307, 2952, 1676, 1449, 1058 cm^{-1}; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_8H_{13}N$, 123.1048; found, 123.1049.



18 *21*

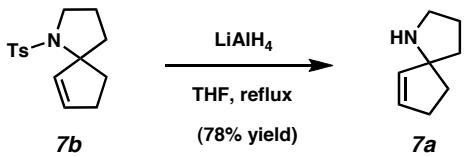
Sulfonamide 21. To a suspension of lithium aluminum hydride (LAH, 5.7 g, 150 mmol) in Et_2O (100 mL) at 0 °C, a solution of ester **18** (16.5 g, 98 mmol) in Et_2O (50 mL) was added dropwise via an addition funnel. After the addition was complete, the reaction was warmed to room temperature and allowed to stir for 19 h. The reaction was then cooled

to 0 °C and quenched by careful addition of H_2O (ca. 50 mL). The resulting mixture was diluted with Et_2O (300 mL) and stirred vigorously with 20% aqueous solution of sodium potassium tartrate (300 mL) for 4 h. The phases were then separated, and the aqueous phase was extracted with Et_2O (4 × 300 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield the alcohol (11.1 g, 88% yield) as a clear oil. The alcohol was taken to the next step without further purification. R_f 0.15 (1:1 hexanes/ CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.32 (m, 1H), 3.59 (m, 1H), 2.57 (br, 1H), 2.26-2.20 (m, 4H), 2.10 (m, 2H), 1.87-1.80 (m, 2H), 1.70-1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 123.8, 62.9, 35.2, 32.6, 30.9, 27.6, 23.6; IR (neat): 3306, 2948, 1652, 1445, 1059 cm^{-1}.

To a solution of alcohol (9.2 g, 73 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (8.12 g, 11.2 mL, 80 mmol), *p*-toluenesulfonyl chloride (TsCl, 15.3 g, 80 mmol), and *N,N*-dimethyl-4-aminopyridine (DMAP, 100 mg, 0.82 mmol) successively at 0 °C. The reaction was allowed to warm to room temperature and stirred for 16 h. The reaction was poured into saturated aqueous NH_4Cl (300 mL). Phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were combined, washed with H_2O (200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (4:1 hexanes/ CH_2Cl_2) to give tosylate (17.1 g, 84% yield) as a clear oil. R_f 0.25 (2:1 hexanes/ CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.20 (m, 1H), 3.98 (t, *J* = 6.3 Hz, 2H), 2.41 (s, 3H), 2.20-2.17 (m, 2H), 2.10-2.02 (m, 4H), 1.78-1.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 142.7, 133.3, 130.0, 128.1, 124.6, 70.5,

35.0, 32.6, 27.1, 26.9, 23.5, 21.8; IR (film): 2950, 1598, 1445, 1361, 1176, 1097 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_{15}H_{20}O_3S$, 280.1133; found, 280.1144.

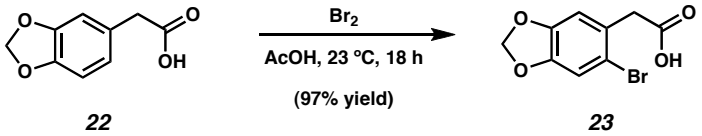
To a solution of tosylate (14.0 g, 49.9 mmol) in CH_3CN (200 mL) was added *p*-toluenesulfonamide (17.1 g, 100 mmol) and K_2CO_3 (13.8 g, 100 mmol) at room temperature. The resulting mixture was heated at 90 °C for 30 h. After cooled the reaction to room temperature, the volatiles were removed in vacuo. The residue was partitioned between H_2O (500 mL) and CH_2Cl_2 (300 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic layers were washed with H_2O (2 × 300 mL), 3 M NaOH (4 × 200 mL), H_2O (200 mL), dried over $MgSO_4$, filtered and concentrated to a yellow oil. The oil was purified by flash chromatography (4:1 hexanes/ EtOAc) to give sulfonamide **21** (13.0 g, 93% yield). R_f 0.20 (4:1 hexanes/ EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 5.23 (m, 1H), 5.03 (t, *J* = 6.0 Hz, 1H), 2.89 (q, *J* = 6.3 Hz, 2H), 2.40 (s, 3H), 2.24-2.19 (m, 2H), 2.13-2.07 (m, 2H), 2.03-1.99 (m, 2H), 1.83-1.75 (m, 2H), 1.63-1.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 143.4, 137.2, 129.9, 127.3, 124.4, 43.2, 35.1, 32.6, 28.2, 27.7, 23.6, 21.7; IR (film): 3284, 2945, 1598, 1438, 1325, 1163, 1095 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{15}H_{21}NO_2S$, 280.1371; found, 280.1372.



7b *7a*

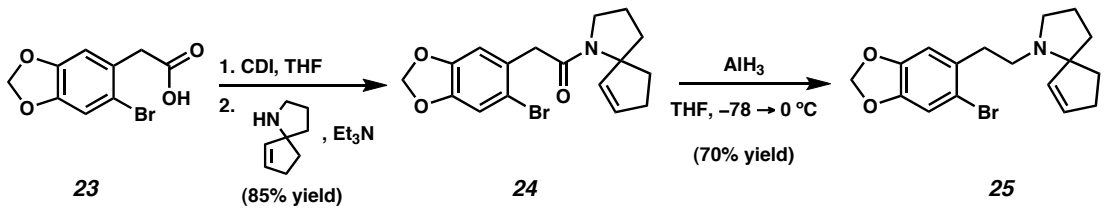
Spiroamine 7a. To a solution of cyclic sulfonamide **7b** (140 mg, 0.5 mmol) in THF (5 mL) was added lithium aluminum hydride (76 mg, 2.0 mmol) at 0 °C. The solution was heated at 70 °C for 12 h. After cooled to room temperature, the reaction was quenched

with H_2O (76 μL), 3 M NaOH (76 μL) and H_2O (228 μL) and stirred for 1 h. The resulting white precipitate was removed by filtration and washed with ether. The filtrate was dried over Na_2SO_4, filtered and concentrated in vacuo to afford the spiroamine **7a** (48 mg, 78% yield) as clear oil. The spiroamine was taken to the next step without further purification.



22 *23*

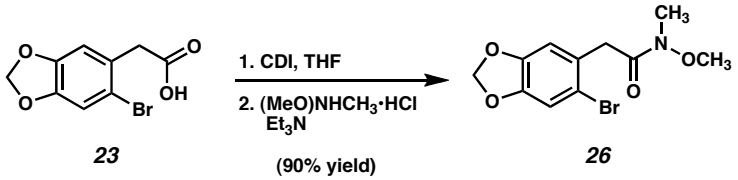
Acid 23. To a solution of 3,4-(methylenedioxy)phenylacetic acid (**22**) (900 mg, 5.0 mmol) in acetic acid (5.0 mL) was added Br_2 (1.6 g, 10.0 mmol) dropwise at room temperature. The resulting solution was stirred at room temperature for 18 h. The reaction was quenched by slow addition of 10% $Na_2S_2O_3$ solution (ca. 1 mL) until the red color disappeared. The mixture was poured into ice water (200 mL) and extracted with Et_2O (4 × 100 mL). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give the desired acid **23** (1.25, 97%) as a white powder. The acid was taken to the next step without further purification. R_f 0.33 (EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.4 (s, 1H), 7.16 (s, 1H), 6.97 (s, 1H), 6.02 (s, 2H), 3.60 (s, 2H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 171.6, 147.2, 147.0, 128.1, 114.9, 112.1, 111.6, 101.9; IR (film): 3400 (br), 1699, 1502, 1488, 1409, 1225 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_9H_7BrO_4$, 257.9528; found, 257.9536.



Tertiary amine 25. To a solution of acid **23** (520 mg, 2.0 mmol) in THF (5.0 mL) was treated with 1,1'-carbonyldiimidazole (CDI, 325 mg, 2.0 mmol) at room temperature. After stirring for 15 min, a solution of spiroamine **7a** (259 mg, 2.1 mmol) in THF (2.0 mL) and triethylamine (212 mg, 2.1 mmol) were added. The resulting solution was stirred at room temperature for 1 h. The reaction was poured into saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (4 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (7:3 hexanes/ EtOAc) to give amide **24** (620 mg, 84.7% yield) as a white powder. R_f 0.30 (1:1 hexanes/ EtOAc); ^1H NMR (300 MHz, $CDCl_3$) showed this compound as a mixture of rotamers in 2:1 ratio, and it is taken to the next step without further characterization.

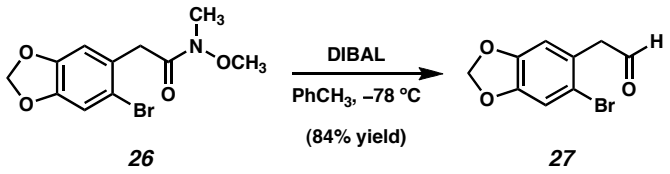
At 0 °C, THF (2.0 mL) was slowly added to a round-bottomed flask charged with aluminum chloride ($AlCl_3$, 16 mg, 0.12 mmol). After the mixture was stirred at this temperature for 5 min, a solution of lithium aluminum hydride (LAH, 14 mg, 0.36 mmol) in THF (1.0 mL) was added dropwise via a syringe. The resulting mixture was stirred for 30 min at room temperature and then cooled to –78 °C. A solution of amide (36.3 mg, 0.1 mmol) in THF (2.0 mL) was added slowly. The reaction was stirred at –78 °C for 45 min, warmed to room temperature and stirred for additional 2 h. The reaction was cooled to 0 °C and quenched by slow addition of 1 N HCl (5.0 mL). The mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were

combined, washed with 1 N NaOH (20 mL), brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (9:1 CH_2Cl_2/MeOH) to yield amine **25** (25 mg, 70% yield) as a lightly yellow oil. R_f 0.20 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (s, 1H), 6.71 (s, 1H), 5.92 (2, 2H), 5.80 (dt, J_1 = 5.7 Hz, J_2 = 2.4 Hz, 1H), 5.56 (dt, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H), 2.98-2.92 (m, 1H), 2.84-2.77 (m, 2H), 2.50-2.42 (m, 2H), 2.30 (tt, J_1 = 6.6 Hz, J_2 = 2.1 Hz, 2H), 1.94-1.82 (m, 4H), 1.63 (app. quintet, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 147.0, 134.3, 133.1, 133.0, 114.6, 112.8, 110.5, 101.8, 78.5, 51.4, 49.8, 38.2, 36.3, 31.7, 29.8, 21.5; IR (film): 2956, 1503, 1478, 1229, 1041 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{17}H_{20}BrNO_2$, 350.0756; found, 350.0748.



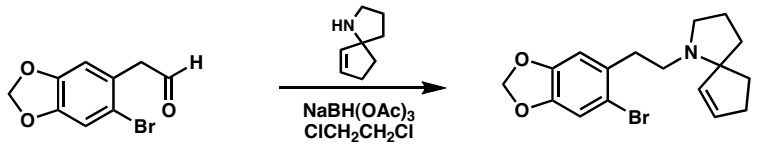
Weinreb amide 26. To a solution of acid **23** (260 mg, 1.0 mmol) in THF (4.0 mL) was treated with 1,1'-carbonyldiimidazole (CDI, 163 mg, 1.0 mmol) at room temperature. After stirring for 15 min, a solution of Weinreb amine hydrochloride salt (108 mg, 1.1 mmol) and triethylamine (303 mg, 3.0 mmol) were added. The resulting solution was stirred at room temperature for 4 h. The reaction was poured into saturated aqueous NH_4Cl (30 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (3:2 hexanes/ EtOAc) to give amide **26** (270 mg, 90% yield) as a white powder. R_f 0.65 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (s, 1H), 6.78 (s, 1H), 5.95 (s, 2H), 3.82 (s, 2H), 3.72 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 171.7, 147.7, 147.6, 128.0, 115.5, 112.9, 111.2, 102.0, 61.6, 39.6, 32.6; IR (film): 2968, 1667, 1503, 1481, 1233, 1037 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{11}H_{12}BrNO_4$, 302.0028; found, 302.0021.



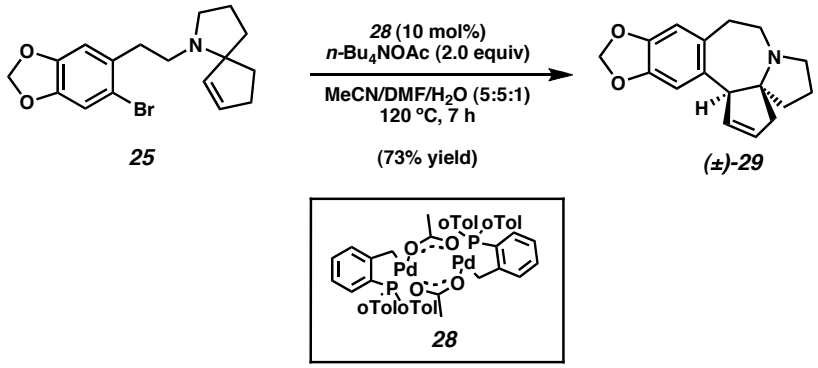
26 *27*

Aldehyde 27. To a solution of Weinreb amide **26** (55 mg, 0.18 mmol) in CH_2Cl_2 (1.0 mL) at –78 °C was added a solution of DIBAL (39 mg, 0.275 mmol) in CH_2Cl_2 (1.0 mL) dropwise. The resulting solution was stirred at –78 °C for 30 min and quenched carefully with MeOH (ca. 0.2 mL). The reaction was poured into CH_2Cl_2 (50 mL), washed with 1 N HCl (10 mL) and brine (10 mL) and the organic layer was quickly passed through a pad of silica gel and concentrated to give the aldehyde **27** (37 mg, 84% yield) as a clear oil. This compound was not stable at room temperature and was taken to the next step immediately. R_f 0.30 (1:4 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 9.73 (t, *J* = 2.0 Hz, 1H), 7.08 (s, 1H), 6.72 (s, 1H), 6.01 (s, 2H), 3.78 (d, *J* = 2.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.6, 148.3, 148.0, 125.5, 115.6, 113.2, 111.3, 102.2, 50.6; IR (film): 2904, 1724, 1503, 1478, 1233, 1038 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_9H_7BrO_3$, 241.9579; found, 241.9569.



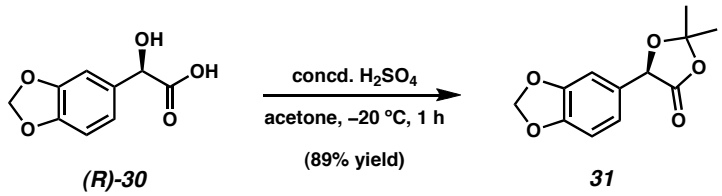
27 *25*

Tertiary amine 25. To a solution of aldehyde **27** (150 mg, 0.62 mmol) and spiroamine **7a** (84 mg, 0.68 mmol) in 1,2-dichloromethane was added sodium triacetoxyborohydride (197 mg, 0.93 mmol) at room temperature. The resulting solution was stirred at room temperature for 24 h and then poured into saturated $NaHCO_3$ (50 mL). The aqueous was extracted with ether (3 × 70 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (1: 9 $MeOH/CH_2Cl_2$) to give amine **25** (183 mg, 85% yield) as a yellow oil.



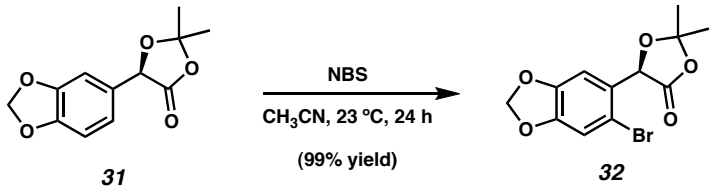
Olefin 29. The amine **25** (70 mg, 0.2 mmol) was dissolved in a mixture of solvents ($DMF/CH_3CN/H_2O$ = 3 mL: 3 mL: 0.6 mL). The solution was degassed with Argon for 15 min and then treated with trans-Di-μ-acetatobis[2-(di-*o*-tolylphosphino)benzyl] dipalladium(II) (21 mg, 0.02 mmol) and tetra-n-butyl ammonium acetate (120 mg, 0.4 mmol). The resulting solution was heated at 120 °C for 7 h. The reaction was cooled to room temperature and filtered through a short pad of celite. The filtrate was concentrated in vacuo. The residue was dissolved in Et_2O (20 mL) and extracted with 1 N NaOH (20 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (EtOAc) to give the olefin **29** (39 mg, 72.5% yield) as a white powder. R_f 0.10 (EtOAc); R_f 0.25 (85:17:1 EtOAc/MeOH/Et_3N); ^1H NMR (300

MHz, $CDCl_3$): δ 6.65 (s, 1H), 6.59 (s, 1H), 5.88 (dd, J_1 = 2.4 Hz, J_2 = 1.5 Hz, 2H), 5.79 (ddd, J_1 = 5.7 Hz, J_2 = 5.4 Hz, J_3 = 2.7 Hz, 1H), 5.52 (ddd, J_1 = 5.7 Hz, J_2 = 4.8 Hz, J_3 = 2.7 Hz, 1H), 3.87 (m, 1H), 3.18 (ddd, J_1 = 14.1 Hz, J_2 = 12.9 Hz, J_3 = 7.2 Hz, 1H), 3.07 (ddd, J_1 = 10.5 Hz, J_2 = 8.7 Hz, J_3 = 4.2 Hz, 1H), 2.74 (ddd, J_1 = 18.0 Hz, J_2 = 4.5 Hz, J_3 = 2.7 Hz, 1H), 2.53 (dd, J_1 = 11.1 Hz, J_2 = 7.2 Hz, 1H), 2.43-2.28 (m, 2H), 2.05-1.93 (m, 3H), 1.80-1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.5, 146.1, 132.5, 132.4, 132.0, 128.9, 111.0, 110.0, 100.9, 68.3, 62.5, 53.8, 49.2, 43.4, 34.9, 30.8, 20.1; IR (film): 2940, 2875, 1502, 1485, 1225, 1039 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{17}H_{19}NO_2$, 270.1484; found, 270.1490.



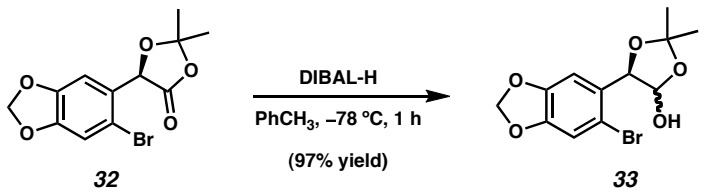
1,3-dioxolanone 31. To a solution of α-hydroxy carboxylic acid (**30**) (1.88 g, 9.6 mmol) in acetone (10 mL) was added concentrated H_2SO_4 (1.0 mL) dropwise at –20 °C. The resulting mixture was stirred at –20 °C for 1 h. The reaction was poured into saturated aqueous $NaHCO_3$ (50 mL) with crushed ice and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to a yellowish oil. The oil was purified by flash chromatography (4:1 hexanes/ EtOAc) to give dioxolanone **31** (2.0 g, 89% yield) as a clear oil. R_f 0.18 (4:1 hexanes/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92-6.88 (m, 2H), 6.80 (dd, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H), 5.93 (s, 2H), 5.27 (s, 1H), 1.67 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 148.5, 148.3, 128.4, 120.9, 110.9, 108.6, 107.2, 101.6, 76.1, 27.4, 26.2; IR (film): 2994, 1794, 1505, 1492, 1446, 1388, 1242, 1118, 1038 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for

$C_{12}H_{12}O_5$, 236.0685; found, 236.0675; $[\alpha]^{25.2}_D$ –70.6° (*c* 1.0, CH_2Cl_2); ee% = 97.5%, Chiralcel OD-H, 1% *i*-PrOH/hexanes, 1 mL/min, T_R = 17.3 min, $T_{R(minor)}$ = 21.4 min.



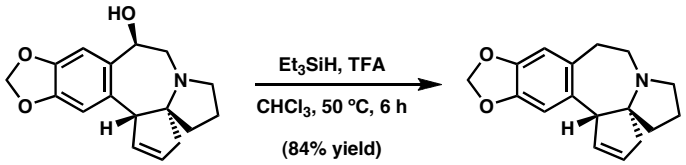
31 *32*

Aryl bromide 32. To a solution of dioxolanone **31** (1.2 g, 5.1 mmol) in acetonitrile (15 mL) was added *N*-bromosuccinamide (1.0 g, 5.6 mmol) at room temperature. The resulting solution was stirred at room temperature in the dark for 24 h. The solution was passed through a pad of silica gel and eluted with CH_2Cl_2 (ca. 100 mL). The filtrate was concentrated to dryness and the residue was purified by flash chromatography (2:1 hexanes/CH_2Cl_2) to give the aryl bromide **32** (1.6 g, 99% yield) as a yellow oil. R_f 0.35 (2:1 hexanes/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04 (s, 1H), 6.84 (s, 1H), 5.99 (dd, J_1 = 5.1 Hz, J_2 = 1.5 Hz, 1H), 5.73 (s, 1H), 1.73 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 149.5, 148.1, 126.7, 115.3, 113.4, 110.9, 108.7, 102.5, 76.0, 27.2, 25.9; IR (film): 2992, 1794, 1504, 1482, 1388, 1238, 1119, 1036 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_{12}H_{11}BrO_5$, 313.9790; found, 313.9794; $[\alpha]^{24.7}_D$ –61.3° (*c* 1.0, CH_2Cl_2); ee% = 97.7%, Chiralcel AD, 1% *i*-PrOH/hexanes, 1 mL/min, T_R = 17.7 min, $T_{R(minor)}$ = 29.4 min.



32 *33*

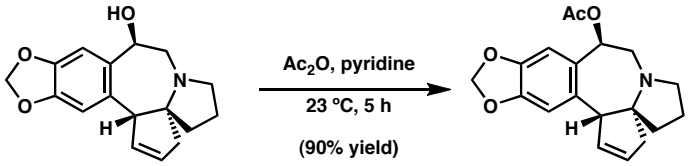
Hemiacetal 33. To a solution of aryl bromide **32** (314 mg, 1.0 mmol) in toluene (4 mL) was added DIBAL (227 mg, 232 μL, 1.6 mmol) dropwise at –78 °C. After stirred at this temperature for 30 min, the reaction was quenched by slow addition of 1 N HCl (2 mL) at –78 °C. The solution was allowed to warm to room temperature and stirred for additional 30 min. The solution was diluted with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were passed through a short pad of silica gel and concentrated in vacuo. The resulting residue was purified by flash chromatography (4:1 hexanes/EtOAc) to give hemiacetal **33** (305 mg, 97% yield) as a mixture of diastereomers in about 1:1 ratio. R_f 0.18 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (s, 1H), 6.99 (s, 1H), 6.98 (s, 1H), 6.97 (s, 1H), 5.99-5.95 (m, 4H), 5.77 (dd, J_1 = 5.1 Hz, J_2 = 3.6 Hz, 1H), 5.33-5.28 (m, 3H), 3.58 (d, J = 3.6 Hz, 1H), 2.73 (d, J = 5.4 Hz, 1H), 1.66 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 147.9, 147.7, 131.5, 129.3, 128.7, 128.5, 125.5, 120.2, 112.9, 112.7, 112.2, 110.1, 109.1, 107.9, 102.1, 101.9, 94.3, 84.3, 81.1, 29.0, 27.8, 27.6, 26.5; IR (film): 3436, 2987, 1502, 1477, 1241, 1038 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_{12}H_{13}BrO_5$, 315.9946; found, 315.9940.



15 *(+)-29*

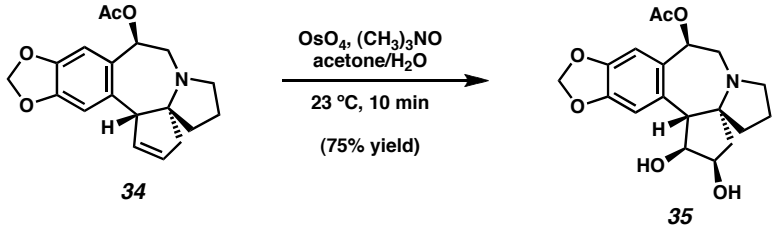
Olefin (+)-29. To a solution of alcohol **15** (8.0 mg, 0.028 mmol) in $CHCl_3$ (1.0 mL) was added trifluoroacetic acid (80 μL, 1 mmol) and Et_3SiH (100 μL, 0.63 mmol). The resulting solution was heated at 50 °C for 6 h and then cooled to room temperature. The

reaction was poured into saturated $NaHCO_3$ (5 mL) and the aqueous was extracted with CH_2Cl_2 (5 × 10 mL). The organics were combined, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by preparative TLC (10% MeOH/ CH_2Cl_2) to give the olefin (+)-**29** (6.4 mg, 84% yield) as a clear oil. The spectra data are identical to those of (±)-**29** presented above. $[\alpha]^{27.3}_D$ +190.5° (*c* 0.15, $CHCl_3$).

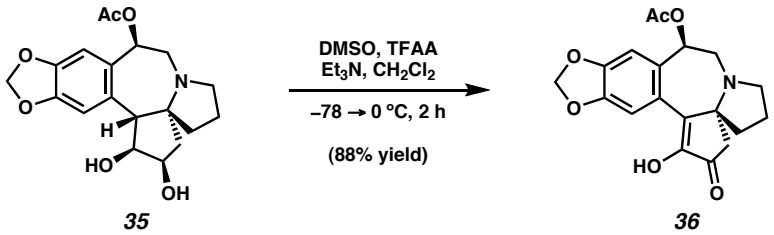


15 ***34***

***anti*-Acetate 34**. The alcohol **15** (67 mg, 0.235 mmol) was dissolved in pyridine (2 mL) and cooled to 0 °C. The solution was treated with acetic anhydride (0.3 mL) and stirred at room temperature for 5 h. The reaction was poured into saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (5 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (1:4 hexanes/EtOAc) to give acetate **34** (70 mg, 90% yield) as a white semi solid. R_f 0.40 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.66 (s, 1H), 6.33 (dd, J_1 = 9.9 Hz, J_2 = 7.2 Hz, 1H) 5.94-5.90 (m, 3H), 5.62-5.58 (m, 1H), 3.92 (t, J = 2.4 Hz, 1H), 3.08-3.00 (m, 1H), 2.89-2.73 (m, 3H), 2.49-2.40 (m, 1H), 2.15 (s, 3H), 2.10-2.03 (m, 1H), 1.98-1.89 (m, 3H), 1.80-1.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 147.0, 146.7, 131.7, 131.4, 129.9, 129.1, 111.2, 104.3, 101.2, 68.8, 68.7, 61.7, 53.1, 52.9, 42.3, 35.5, 21.3, 20.2; IR (film): 2882, 1741, 1502, 1485, 1369, 1236, 1038 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_{19}H_{21}NO_4$, 327.1471; found, 327.1468; $[\alpha]^{24.7}_D$ +42.2° (*c* 1.0, $CHCl_3$).

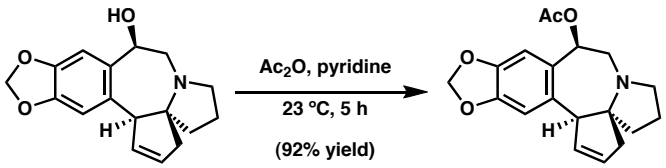


***anti*-Diol 35**. To a solution of olefin **34** (40 mg, 0.122 mmol) in acetone (2.0 mL) was added trimethylamine *N*-oxide (13.8 mg, 0.184 mmol, 1.5 equiv) at room temperature. A freshly made solution of OsO_4 (1.55 mg, 0.006 mmol, 5 mol%) in H_2O (1.0 mL) was added and the reaction was stirred at room temperature for 10 min. Sodium sulfite (Na_2SO_3, 0.3 g) was added to the solution and the mixture was stirred at room temperature for 30 min. Most volatiles were removed in vacuo and the residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL). The aqueous phase was further extracted with CH_2Cl_2 (4 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to give diol **35** (33 mg, 75% yield) as a white powder. R_f 0.40 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (s, 1H), 6.65 (s, 1H), 6.02 (dd, J_1 = 10.2 Hz, J_2 = 7.8 Hz, 1H), 5.93 (s, 2H), 4.50 (dd, J_1 = 9.3 Hz, J_2 = 3.9 Hz, 1H), 4.29 (t, J = 3.6 Hz, 1H), 3.12 (d, J = 9.6 Hz, 1H), 3.05-2.98 (m, 1H), 2.89-2.77 (m, 2H), 2.51-2.35 (m, 3H), 2.20 (s, 3H), 2.14-2.03 (m, 2H), 1.77-1.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 147.2, 146.8, 130.2, 129.8, 112.3, 104.7, 101.3, 77.9, 72.5, 68.7, 67.0, 59.8, 53.7, 52.3, 43.9, 31.1, 21.3, 19.7; IR (film): 3400, 2929, 1741, 1503, 1486, 1371, 1237, 1038 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{19}H_{23}NO_6$, 362.1604; found, 362.1588; $[\alpha]^{25.6}_D$ –6.3° (*c* 1.0, CH_2Cl_2).

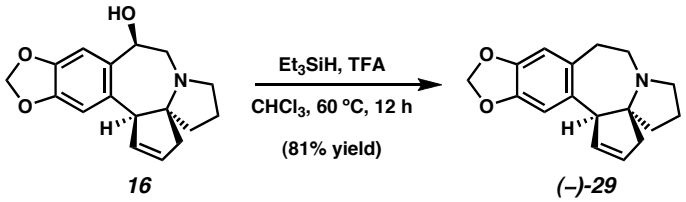


35 ***36***

***anti*-Dione 36**. DMSO (60 mg, 55 μL, 0.77 mmol) was dissolved in CH_2Cl_2 (3 mL). At –78 °C, trifluoroacetic anhydride (TFAA, 46 mg, 30 μL, 0.22 mmol) was added slowly. The resulting solution was stirred at –78 °C for 10 min and then treated with a solution of diol **35** (20 mg, 0.055 mmol) in CH_2Cl_2 (1 mL) dropwise. The reaction was allowed to stir at –78 °C for 1.5 h and then treated with Et_3N (90 mg, 124 μL, 0.88 mmol). The solution was warmed to 0 °C and stirred for 30 min. The reaction was quenched with water (15 mL) and diluted with CH_2Cl_2 (20 mL). The aqueous phase was further extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by preparative TLC (12:1 CH_2Cl_2/MeOH) to yield dione **36** (17.3 mg, 88% yield) as a white solid. R_f 0.70 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.77 (s, 1H), 6.15 (t, J = 4.5 Hz, 1H), 6.00 (dd, J_1 = 6.3 Hz, J_2 = 1.5 Hz, 2H), 3.45 (A part of ABX, J_1 = 16.2 Hz, J_2 = 3.3 Hz, 1H), 3.23-3.16 (m, 2H), 3.04-2.98 (m, 1H), 2.55 (q, J = 18.0 Hz, 2H), 2.19 (s, 3H), 2.03-1.93 (m, 2H), 1.81-1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 170.7, 148.9, 147.7, 147.5, 144.7, 130.8, 124.1, 109.7, 109.0, 102.0, 71.2, 69.9, 52.4, 50.1, 48.9, 39.6, 24.6, 21.7; IR (film): 3400, 2927, 1733, 1707, 1505, 1486, 1370, 1238 cm^{-1}; HRMS-FAB (m/z): $[M + H]^+$ calc'd for $C_{19}H_{19}NO_6$, 358.1291; found, 358.1285; $[\alpha]^{24.8}_D$ –152.2° (*c* 0.7, $CHCl_3$).

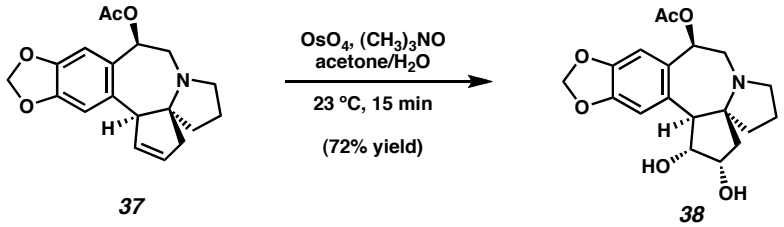


***syn*-Acetate 37**. The crude product of Heck reaction was dissolved in CH_2Cl_2 (3 mL) and pyridine (1 mL) and cooled to 0 °C. The solution was treated with acetic anhydride (1 mL) and stirred at room temperature for 5 h. The reaction was poured into saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (5 × 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (3:7 hexanes/EtOAc→1:9 hexanes/EtOAc) to give acetate **37** (116 mg, 65% yield over two steps) as a white semi solid. R_f 0.24 (EtOAc); R_f 0.45 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (s, 1H), 6.72 (s, 1H), 5.93-5.91 (m, 2H), 5.86 (q, J = 4.5 Hz, 1H), 5.75 (m 2H), 3.85 (d, J = 1.5 Hz), 3.31 (dd, J_1 = 14.1 Hz, J_2 = 8.7 Hz, 1H), 2.89-2.82 (m, 1H), 2.75-2.62 (m, 2H), 2.47 (d, J = 17.7 Hz, 1H), 2.15 (app. dd, J_1 = 17.7 Hz, J_2 = 1.8 Hz, 1H), 2.01 (s, 3H), 1.93-1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 147.7, 146.6, 134.8, 133.7, 129.5, 127.7, 111.2, 111.0, 101.4, 75.1, 71.5, 59.1, 52.4, 51.9, 38.9, 38.6, 21.7, 20.7; IR (film): 2959, 1728, 1506, 1489, 1370, 1234, 1041 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{19}H_{21}NO_4$, 328.1549; found, 328.1563; $[\alpha]^{24.9}_D$ –68.3° (*c* 1.0, $CHCl_3$).



Olefin (–)-29. To a solution of alcohol **16** (5.6 mg, 0.019 mmol) in $CHCl_3$ (1.0 mL) was added trifluoroacetic acid (80 μL, 1 mmol) and Et_3SiH (100 μL, 0.63 mmol). The

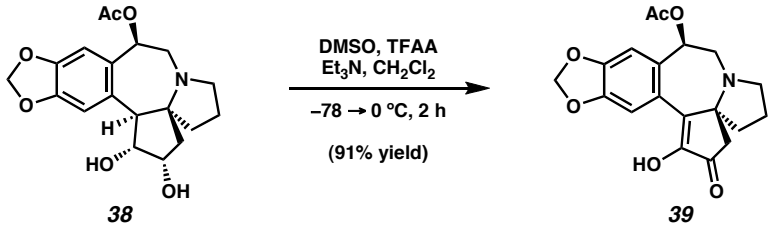
resulting solution was heated at 60 °C for 12 h and then cooled to room temperature. The reaction was poured into saturated $NaHCO_3$ (5 mL) and the aqueous was extracted with CH_2Cl_2 (5 × 10 mL). The organics were combined, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by preparative TLC (15% MeOH/ CH_2Cl_2) to give the olefin (–)-**29**(4.0 mg, 81% yield) as a clear oil. The spectra data are identical to those of (±)-**29** presented above. $[\alpha]^{22.8}_D$ –201.2° (*c* 0.19, $CHCl_3$).



37 *38*

***syn*-Diol 38**. To a solution of olefin **37** (78 mg, 0.238 mmol) in acetone (3.0 mL) was added trimethylamine *N*-oxide (26.9 mg, 0.359 mmol, 1.5 equiv) at room temperature. A freshly made solution of OsO_4 (3 mg, 0.012 mmol, 5 mol%) in H_2O (1.0 mL) was added and the reaction was stirred at room temperature for 10 min. Sodium sulfite (Na_2SO_3, 0.5 g) was added to the solution and the mixture was stirred at room temperature for 30 min. Most volatiles were removed in vacuo and the residue was partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was further extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to give diol **38** (58 mg, 72% yield) as a white powder. R_f 0.35 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.67 (s, 1H), 5.99 (dd, J_1 = 8.7 Hz, J_2 = 3.0 Hz, 1H), 5.91 (dd, J_1 = 3.6 Hz, J_2 = 1.8 Hz, 2H), 4.52 (dd, J_1 = 10.2 Hz, J_2 = 4.5 Hz, 1H), 4.24 (t, *J*

= 4.2 Hz, 1H), 3.45 (dd, J_1 = 15.3 Hz, J_2 = 9.0 Hz, 1H), 3.17 (d, J = 10.2 Hz, 1H), 2.91 (app. q, J = 4.2 Hz, 1H), 2.74 (dd, J_1 = 15.0 Hz, J_2 = 2.7 Hz, 1H), 2.52 (q, J = 7.5 Hz, 2H), 2.20-2.10 (m, 3H), 2.00 (s, 3H), 1.83-1.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 148.0, 146.8, 133.9, 128.4, 113.7, 113.4, 101.6, 80.4, 76.2, 72.3, 68.2, 60.3, 52.8, 51.1, 42.3, 34.3, 21.8, 20.4; IR (film): 3413, 2930, 1735, 1506, 1489, 1371, 1232 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{19}H_{23}NO_6$, 362.1604; found, 362.1591; $[\alpha]^{24.4}_D$ –9.6° (*c* 1.0, CH_2Cl_2).



38 ***39***

***syn*-Dione 39**. DMSO (120 mg, 109 μL, 1.54 mmol) was dissolved in CH_2Cl_2 (5 mL). At –78 °C, trifluoroacetic anhydride (TFAA, 92.4 mg, 61 μL, 0.44 mmol) was added slowly. The resulting solution was stirred at –78 °C for 10 min and then treated with a solution of diol **38** (40 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) dropwise. The reaction was allowed to stir at –78 °C for 1.5 h and then treated with Et_3N (178 mg, 245 μL, 1.76 mmol). The solution was warmed to 0 °C and stirred for 30 min. The reaction was quenched with water (15 mL) and diluted with CH_2Cl_2 (20 mL). The aqueous phase was further extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by preparative TLC (12:1 CH_2Cl_2/MeOH) to yield dione **39** (36 mg, 91% yield) as a white powder. R_f 0.60 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.86 (s, 1H), 6.35 (dd, J_1 = 10.2 Hz, J_2 = 6.0 Hz, 1H), 6.01 (d, J = 6.6 Hz, 2H), 3.29 (A part of ABX, J_1 =

15.0 Hz, J_2 = 6.0 Hz, 1H), 3.12 (B part of ABX, J_1 = 15.0 Hz, J_2 = 10.0 Hz, 1H), 3.10-3.05 (m, 1H), 2.90-2.84 (m, 1H), 2.58 (q, J = 18.6 Hz, 2H), 2.04 (s, 3H), 1.87-1.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3, 170.6, 148.7, 148.0, 147.7, 143.8, 130.6, 124.9, 111.2, 109.8, 101.9, 71.9, 69.5, 50.9, 50.3, 47.2, 40.0, 24.8, 21.5; IR (film): 3307, 2929, 1725, 1704, 1504, 1487, 1383, 1234 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{19}H_{19}NO_6$, 358.1291; found, 358.1297; $[\alpha]^{25.0}_D$ +131.8° (*c* 1.0, CH_2Cl_2).